Current Trends in Mass Spectroscopy, 11/06

- Donald Rumsfeld (US Secretary of Defense)

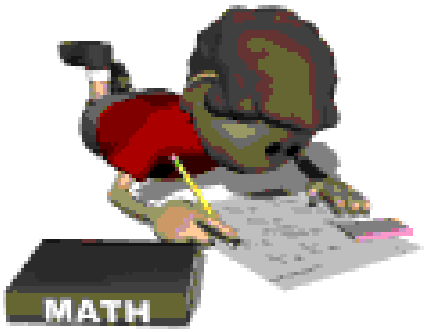
There are known knowns. These things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

Establishing Matrix Spike (MS) Control Limits from Laboratory Control Samples (LCSs)

What I didn't know that I didn't know about matrix spikes

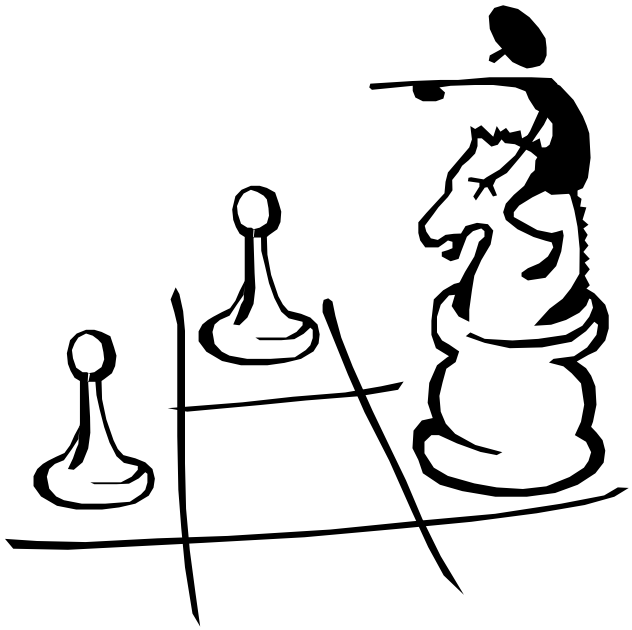
Thomas J. Georgian, Ph.D.
HTRW CX
Omaha, NE

US Army Corps of Engineers ®



Major Objective of Matrix Spike (MS) Recovery Data

- Determine if a matrix effect (interference) exists and whether it is unacceptably large.



SW-846 (Method 8000C)

- Compliance Monitoring: Spike site-specific background samples at higher of 1 – 5x native analyte concentration or action level.
- Other monitoring: Spike at 20x LOQ or near mid-calibration range.
- Use 15 - 20 pts. to calculate control limits (CLs)

  ‹R› +/- 3 s

  ‹R› = mean MS recovery

  s = standard deviation

Problem with SW-846 Approach

- Not practical !
  - It is costly to develop MS CLs using site specific background samples.
  - Spike levels cannot be readily adjusted to 1 - 5x native conc. or project action levels.

Commercial Laboratories

- Spike between low and mid-calibration range; generate CLs by pooling MS recoveries from different batches of environmental samples.
  - Entails use of MS recoveries from different sites and matrices that contain interferences !
  - Results in wide unrepresentative CLs for determination of presence of matrix effects.

DoD Quality Systems Manual (QSM)

- Spike 1 - 4x native analyte conc. or below mid-calibration range.
- Evaluate MS recoveries using laboratory control sample (LCS) acceptance ranges in DoD QSM (statistical control limits established from multiple laboratories).

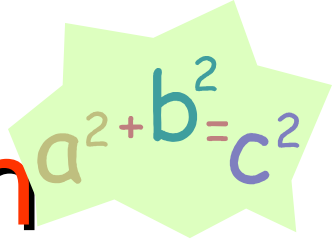
Disadvantages

- Not practical to adjust spiking concentration to 1 - 4x native concentration.
- Not optimal to equate MS control limits (CLs) to the LCS CLs.
  - Pooled multi-lab LCS CLs often wider than single lab in-house LCS CLs.
  - **Single-lab MS CLs inherently wider than LCS CLs.**

Proposed Approach

- Use native analyte conc. to adjust MS acceptance range rather than the MS spike conc.
- Use single-lab in-house LCS CLs to calculate MS acceptance range.

Theory & Derivation



- Visualize MS recovery as being calculated from *two measurements* in a "clean" matrix.

C_I = measured native or initial sample conc.

C_F = measured final conc. after MS spike, C_S

$$R = 100\,(C_F - C_I)/C_S$$

$R \pm 3\,\sigma_R$ - "True" MS CLs

Population mean

Population standard deviation

Derivation

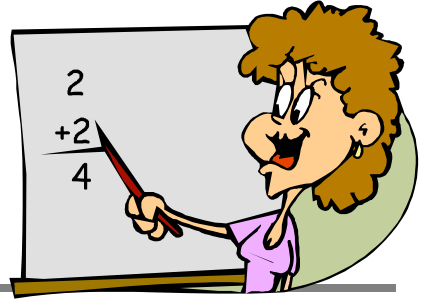
- Bias: “True” MS Recovery, R = Mean LCS recovery, R_{LCS}
- Precision: Std. dev. of R (propagate error):

$$\sigma_R = (100/ C_S) [\sigma_F^2 + \sigma_I^2]^{½}$$

- Assume relative error is constant:

$$\sigma_F /C_F = \sigma_I /C_I = \sigma_{LCS}/R_{LCS}$$

Derivation



- Therefore, MS CL range is:

$$R_{LCS} \pm 3\,\sigma_{LCS}\,[100/(R_{LCS}\,C_S)]\,[C_F^2 + C_I^2]^{1/2}$$

Note:

(1) MS control range wider than LCS control range.

(2) When $C_I = 0$, $[100/(R_{LCS}\,C_S)]\,[C_F^2 + C_I^2]^{1/2} = 1$.

Derivation

- Define

  $k = C_I/C_S$ = ratio of native to MS spike conc.

- Therefore:

$$C_I = k\, C_S$$

$$C_F \approx C_I + C_S = k\, C_S + C_S = C_s\,(k + 1)$$

$$R_{LCS} \pm 3\,\sigma_{LCS}\,[100/R_{LCS}]\,[(1+ k)^2 + k^2]^{½}$$

Approximate Solution

- Assume bias is small: $100/(R_{LCS}) \approx 1$
- If $k \leq 0.5$, then $[(1 + k)^2 + k^2]^{½} \approx 1 + k$
- Therefore, MS CL range is:

$$R_{LCS} \text{ +/- } 3\ \sigma_{LCS}\,(1 + k),\ \ k = C_I / C_S \leq 0.5$$

$$\langle R_{LCS} \rangle \text{ +/- } 3\ s_{LCS}\,(1 + k'),\ \ k' = C'_I / C_S \leq 0.5$$

Example - Metals

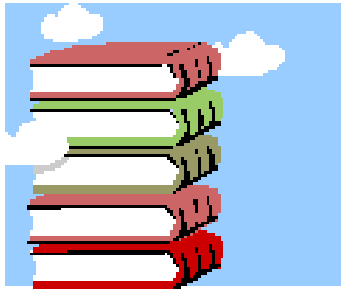
LCS CLs = 80% - 120% → 100 +/- 20%

k' = 0.25

Calculated MS acceptance range:

100 +/- 20% (1 + 0.25) = 75% - 125%

Inorganic National Functional Guidelines



…spike recovery limits do not apply when the sample conc. is ≥ 4x the spike added…

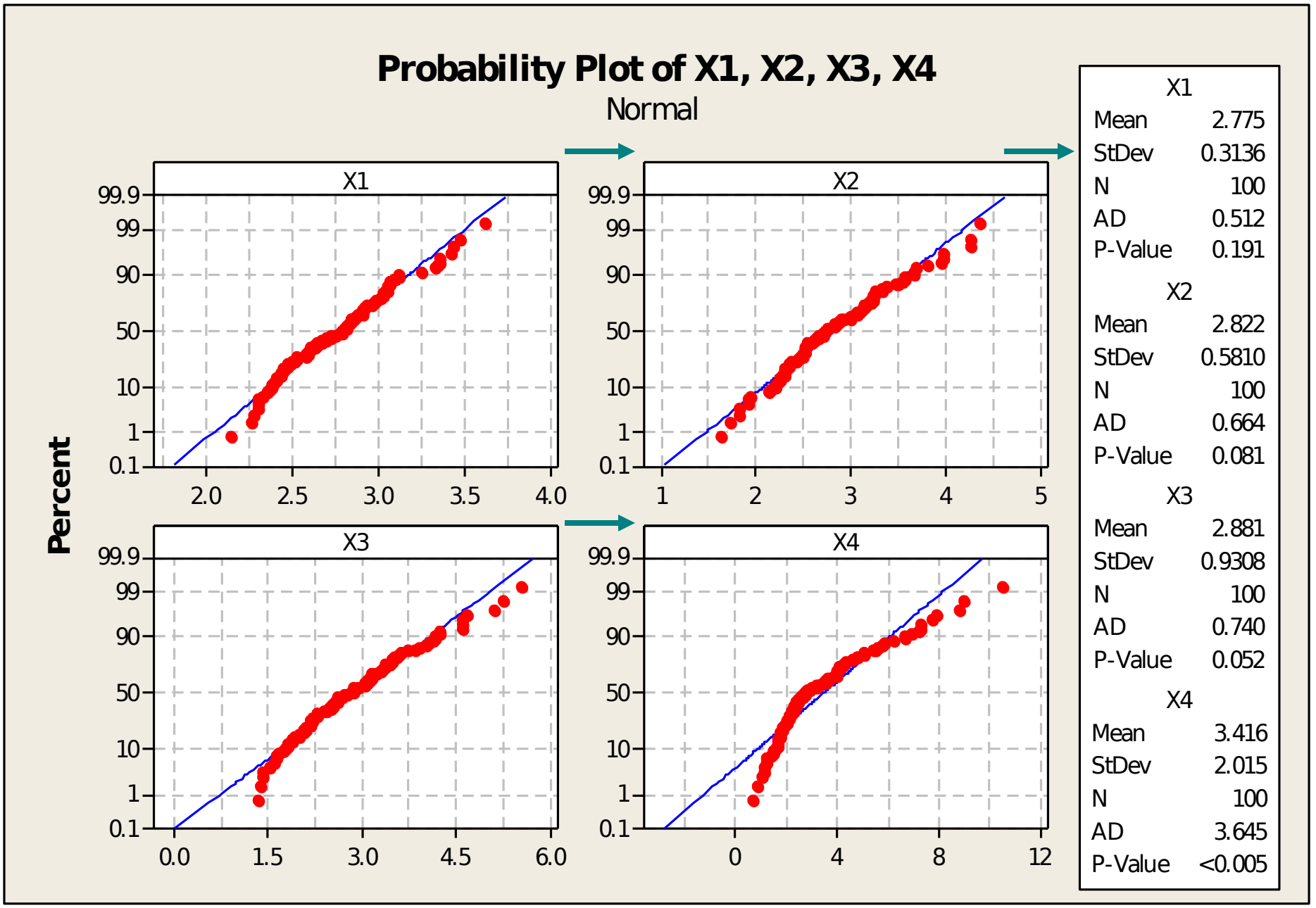
A better requirement would be:

…spike recovery limits do not apply when the sample conc. is ≥ ***¼ x*** *the spike added…*

Caution

- Assumptons:
  - Normality
  - Relative error is constant ($\sigma \propto$ Conc.)
  - No significant bias *
  - Spike conc. $\geq$ 2x native conc. *
- Not recommended if σ_{LCS}/R_{LCS} > 20% - 30%, as normality assumption may be violated:

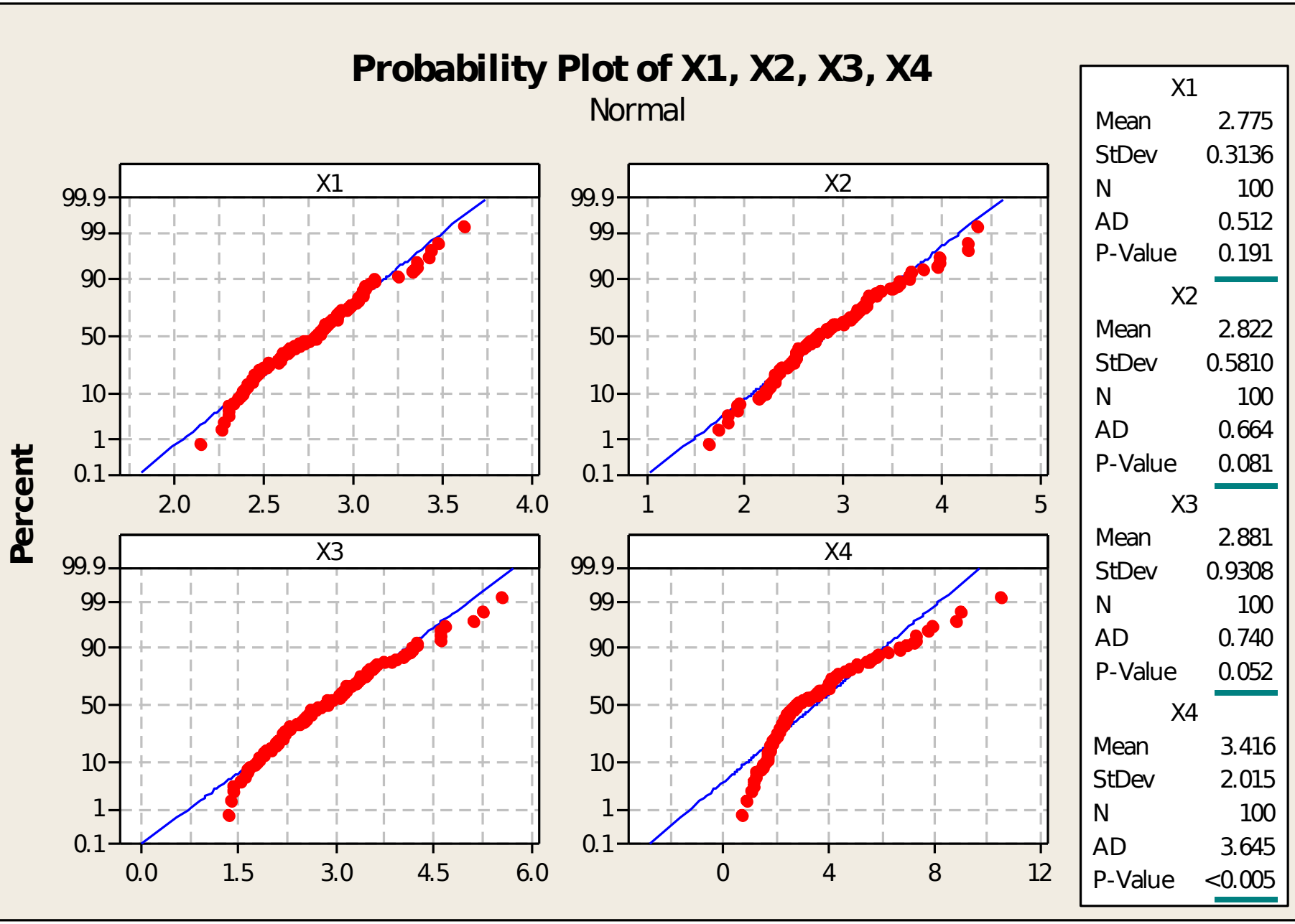
*** Required for approximation.**



σ/μ = 10% → 20% → 30% → 60%

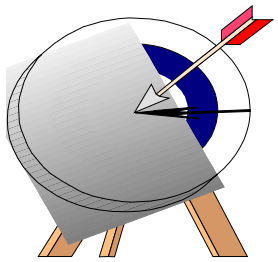
P-value

The probability value associated with a statistical test, representing the likelihood that a test statistic would assume or exceed a certain value by chance, assuming the null hypothesis is true.



σ/μ = 10% → 20% → 30% → 60%

Conclusions



- MS CLs are inherently wider than in-house LCS CLs (even when there are no interferences) by a factor of about 1+ k,

  k = native conc./spike conc.

- Use in-house LCS CLs when k is small (e.g., the spike conc. is 5 - 10x the native analyte conc).